PATENT
Attorney Docket No.: 015280-358100US
Client Ref. No.: E-223-1998/0-US-03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

AMBS and HARRIS

Application No.: 09/830,977

Filed: July 31, 2001

For: P53 AND VEGF REGULATE TUMOR GROWTH OF NOS2 EXPRESSING CANCER CELLS

Customer No.: 20350

Confirmation No. 7226

Examiner: Sheela Jitendra Huff

Technology Center/Art Unit: 1642

Declaration of Stefan Ambs and Curtis C. Harris pursuant to 37 C. F. R. §1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

We, Stefan Ambs and Curtis C. Harris, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. §1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of our own knowledge are true and statements made on information or belief are believed to be true. This declaration is made further to the 37 C.F.R. §1:131declaration submitted August 3, 2004, the contents of which are incorporated herein by reference.

2. We are the named inventors on this application. We have read the application and are familiar with its contents. We have also read the final Office Action mailed August 31, 2004, for this application. It is our understanding that the Examiner believes that the pending claims are anticipated by Rieger *et al.* (*Oncogene* 1998, **17**:2323-2332). The Examiner apparently takes the position that the 37 C.F.R. §1.131declaration and accompanying evidence submitted August 3, 2004, have not properly antedated the cited reference, based on two reasons: first, the evidence does not show contemplation of the claimed screening process for compounds regulating NOS2 expression; and second, the evidence shows a species of NOS2 inhibitor, aminoguanidine (AG), that is different from the species described in the references, such as cytokines and lipopolysaccharide (LPS).

3. This declaration is provided to establish that the conception and completion of the claimed screening process took place at the same time when the underlying invention was first made and that the completion of the claimed invention is naturally and logically associated with the experiments shown in the evidence. This declaration is provided to further establish that in light of the effect of NOS2 on p53-deficient tumor cell growth illustrated by the present application, it would be obvious for one of skill in the art to regulate tumor growth in p53-deficient cells using any compounds capable of modulating NOS2 activity, regardless the identity of such compounds.

4. As the 37 C.F.R. §1.131 declaration submitted August 3, 2004, has established, we completed the claimed invention in the United States prior to November 5, 1998, the publication date under 35 U.S.C. §102(a) for the Rieger *et al.* reference. We hereby further state that the use of p53-deficient cells to screen for NOS2 modulators was simultaneously conceived and completed when the invention in evidence was made. The use of p53-deficient cells for screening purpose is an integral part and a logical permutation of the invention in evidence. Because the invention in the evidence indicates a growth-promoting effect by NOS2 in p53-deficient tumor cells that can be reversed by an inhibitor of NOS2, one of ordinary skill in the art would therefore immediately recognize that p53-deficient cells can be used for the identification of NOS2 modulators. Also, because the very same assay system as shown in the

evidence can be used for this screening process, the invention as presently claimed was not only conceived but also completed prior to November 5, 1998.

5. The claimed invention relates to a method for identifying compounds capable of regulating NOS2 expression, using cells that lack functional p53 protein. The claimed method is therefore useful for screening any compound that could potentially modulate NOS2 expression and is certainly not limited to any particular NOS2 modulator. Although this invention is based on the observation that one particular NOS2 inhibitor, aminoguanidine (AG), can reverse the growth-promoting effect of NOS2 in p53-deficient cells, the general mechanism of regulating NOS2's effect on tumor growth in p53-deficient cells, as illustrated by this observation, is applicable to any and all NOS2 modulators. Thus, when the use of a NOS2 modulator is concerned, the use of NOS2 modulators beyond the exemplary species used this application would be obvious to one of skill in the art.

6. In light of the forgoing, Applicants submit that the invention as claimed was completed before the effective date of the Rieger *et al.* reference, and that the use of other NOS2 modulators not named in the evidence submitted with the declaration of August 3, 2004, would be obvious to a person of skill in the art in light of the general mechanism illustrated by the present invention.

7. Declarants have nothing further to say.

Dated: 12/5/2004 By: _____
Stefan Ambs, Ph.D.

Dated: _____ By: _____
Curtis C. Harris, M.D.

60357955 V1

evidence can be used for this screening process, the invention as presently claimed was not only conceived but also completed prior to November 5, 1998.

5. The claimed invention relates to a method for identifying compounds capable of regulating NOS2 expression, using cells that lack functional p53 protein. The claimed method is therefore useful for screening any compound that could potentially modulate NOS2 expression and is certainly not limited to any particular NOS2 modulator. Although this invention is based on the observation that one particular NOS2 inhibitor, aminoguanidine (AG), can reverse the growth-promoting effect of NOS2 in p53-deficient cells, the general mechanism of regulating NOS2's effect on tumor growth in p53-deficient cells, as illustrated by this observation, is applicable to any and all NOS2 modulators. Thus, when the use of a NOS2 modulator is concerned, the use of NOS2 modulators beyond the exemplary species used this application would be obvious to one of skill in the art.

6. In light of the forgoing, Applicants submit that the invention as claimed was completed before the effective date of the Rieger *et al.* reference, and that the use of other NOS2 modulators not named in the evidence submitted with the declaration of August 3, 2004, would be obvious to a person of skill in the art in light of the general mechanism illustrated by the present invention.

7. Declarants have nothing further to say.

Dated: _____ By: _____
Stefan Ambs, Ph.D.

Dated: 12/11/04 By: _____
Curtis C. Harris, M.D.

60357955 V1